Apixaban compared with parenteral heparin and/or vitamin K antagonist in patients with nonvalvular atrial fibrillation undergoing cardioversion

Ezekowitz, Michael D.; Pollack, Charles V.; Sanders, Paul; Halperin, Jonathan L.; Spahr, Judith; Cater, Nilo; Petkun, William; Breazna, Andrei; Kirchhof, Paulus; Oldgren, Jonas

DOI:
10.1016/j.ahj.2016.06.008

Document Version
Peer reviewed version

Citation for published version (Harvard):
Ezekowitz, MD, Pollack, CV, Sanders, P, Halperin, JL, Spahr, J, Cater, N, Petkun, W, Breazna, A, Kirchhof, P & Oldgren, J 2016, 'Apixaban compared with parenteral heparin and/or vitamin K antagonist in patients with nonvalvular atrial fibrillation undergoing cardioversion: Rationale and design of the EMANATE trial', *American Heart Journal*, vol. 179, pp. 59-68. https://doi.org/10.1016/j.ahj.2016.06.008

Apixaban compared with parenteral heparin and or Vitamin K antagonist in patients with non-valvular atrial fibrillation undergoing cardioversion: Rationale and design of the EMANATE Trial

Michael D. Ezekowitz MBChB, DPhil, Charles V. Pollack MD, MA, Paul Sanders PhD, Jonathan L. Halperin MD, Judith Spahr MPH, MEd, Nilo Cater MD, William Petkun MD, Andrei Breazna PhD, Paulus Kirchhof MD, Jonas Oldgren MD, PhD

PII: S0002-8703(16)30097-7
DOI: doi: 10.1016/j.ahj.2016.06.008
Reference: YMHJ 5211

To appear in: *American Heart Journal*

Received date: 18 January 2016
Accepted date: 15 June 2016

Please cite this article as: Ezekowitz Michael D., Pollack Charles V., Sanders Paul, Halperin Jonathan L., Spahr Judith, Cater Nilo, Petkun William, Breazna Andrei, Kirchhof Paulus, Oldgren Jonas, Apixaban compared with parenteral heparin and or Vitamin K antagonist in patients with non-valvular atrial fibrillation undergoing cardioversion: Rationale and design of the EMANATE Trial, *American Heart Journal* (2016), doi: 10.1016/j.ahj.2016.06.008

Revision June 10, 2016

SHORT TITLE **Rationale and design of the EMANATE Trial**

Apixaban compared with parenteral heparin and or Vitamin K antagonist in patients with non-valvular atrial fibrillation undergoing cardioversion: Rationale and design of the EMANATE Trial

Michael D. Ezekowitz MBChB, DPhil[a]; Charles V. Pollack, MD, MA[b]; Paul Sanders, PhD[c] , Jonathan L. Halperin, MD[d]; Judith Spahr MPH, MEd[e], Nilo Cater, MD[f]; William Petkun, MD[g]; Andrei Breazna, PhD[f]; Paulus Kirchhof, MD[h] Jonas Oldgren MD, PhD[i]

[a]Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, USA and Lankenau Medical Center, Wynnewood, USA; [b] Thomas Jefferson University, Philadelphia, USA; [c] Pfizer, London, UK; [d] Icahn School of Medicine at Mount Sinai, NY, USA; [e] Lankenau Institute for Medical Research, Wynnewood, USA; [f] Pfizer, NYC, USA; [g] Bristol-Myers-Squibb Inc, Princeton, USA; [h]University of Birmingham Institute of Cardiovascular Sciences, SWBH and UHB NHS trusts, Birmingham, United Kingdom, and Department of Cardiology and Angiology, University Hospital Münster, Münster, Germany; [i]Uppsala Clinical Research Centre, and Dept. of Medical Sciences, Uppsala University, Uppsala, Sweden

Corresponding author:

Michael Ezekowitz, MD, PhD

michael.ezekowitz@comcast.net

1999 Sproul Rd, Broomall, PA 19008

215-514-5790

ABSTRACT

Background: Stroke prevention in anticoagulation-naïve patients with atrial fibrillation undergoing cardioversion has not been systematically studied.

Objective: To determine outcomes in anticoagulation-naïve patients (defined as those receiving an anticoagulant for <48 hours during the index episode of AF) scheduled for cardioversion.

Methods: This is a randomized, prospective, open-label, real world study comparing apixaban to heparin plus warfarin. Early image-guided cardioversion is encouraged. For apixaban, the usual dose is 5 mg BID with a dose reduction to 2.5 mg BID if two of the following are present: age≥ 80 years, weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL. If cardioversion is immediate, a single starting dose of 10 mg (or 5 mg if the dose is down-titrated) of apixaban is administered. Cardioversion may be attempted up to 90 days after randomization. Patients are followed for 30 days following cardioversion or 90 days post-randomization if cardioversion is not performed within that timeframe. Outcomes are stroke, systemic embolization, major bleeds, clinically relevant non-major bleeding, and death, all adjudication–blinded.

Statistics: The warfarin-naive cohort from the ARISTOTLE study was considered the closest data set to the patients being recruited into this study. The predicted incidence of stroke, systemic embolism, and major bleeding within 30 days after randomization was approximately 0.75%. To adequately power for a non–inferiority trial, approximately 48,000 subjects would be needed, a number in excess of feasibility. The figure of 1,500 patients was considered clinically meaningful and achievable.

Clinical context: This first prospective cardioversion study of a novel anticoagulant in anticoagulation-naïve patients should influence clinical practice.

Trial registration number **NCT02100228**

Abstract: 257 words

Keywords: Atrial fibrillation, apixaban, anticoagulation, cardioversion, prospective

INTRODUCTION

Non-valvular atrial fibrillation (NVAF) is a modern epidemic affecting 1 in 4 adults aged 60 years and older.[1] Electrical or pharmacological cardioversion or both together are standard practice for restoring sinus rhythm in selected patients with persistent AF.[2] The risk of peri - procedural thromboembolism may exceed 5% when anticoagulation is inadequate.[3,4] Therapeutic anticoagulation with a vitamin K antagonist (VKA) reduces the risk to less than 1%.[5-7] Current practice guidelines recommend anticoagulation for at least 3 weeks before and at least 4 weeks after cardioversion for patients with AF lasting more than 48 hours or when the duration is uncertain.[2,8,9] Secondary post hoc analyses of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY trial)[7], the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE trial),[10] and the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF trial)[11] suggest that the non-VKA oral anticoagulants (NOACs) may be a reasonable alternative to heparin and warfarin for patients with NVAF undergoing cardioversion and that event rates are very low (**Table 1**). The major limitation of these post hoc analyses, however, is the prolonged period of anticoagulation preceding the cardioversion. The need for more immediate cardioversion frequently arises in patients presenting with newly identified atrial fibrillation. The eXplore the efficacy and safety of once-daily oral riVaroxaban for prEvention of caRdiovascular events in Patients with nonvalvular aTrial fibrillation (X-VeRT) trial[12] was the first prospective trial of a NOAC in the setting of cardioversion and found rivaroxaban, an oral factor Xa inhibitor, comparable to VKA in patients with NVAF undergoing cardioversion within 5 days or after 3 weeks and up to a maximum of 8 weeks of anticoagulation, once again with very low event rates (0.5 and 0.6 % for efficacy and safety for rivaroxaban and 1.0 and 0.8 % for usual therapy , both not significantly different). No studies have specifically evaluated a NOAC in a population of patients who are anticoagulation-naïve who are undergoing cardioversion. EMANATE will uniquely address cardioversion in this population.

Apixaban

Apixaban is an orally active, reversible, direct inhibitor of human coagulation Factor Xa (FXa) developed jointly by Bristol-Myers Squibb (BMS) and Pfizer as an anti-thrombotic agent, now

licensed globally for the prevention of stroke and systemic embolization in patient with NVAF and for treatment and prevention of venous and thromboembolic disease.[13]

OBJECTIVES

The goal of this study is to assess clinical outcomes in patients randomized to apixaban against conventional anticoagulant care (parenteral heparin and/or a VKA) in patients with recently detected AF considered for cardioversion. The protocol encourages an image-guided approach (transesophageal echocardiography or computerized tomography), or anticoagulation for a minimum of 3 weeks prior to cardioversion.[2,8] To avoid confounding by prior treatment, the study focuses on patients who are anticoagulation-naïve, excluding patients receiving any anticoagulant for >48 hours during the index episode of AF. Another aim of the study is to define predictors of a successful outcome at 30 days after cardioversion.

DESIGN

This is a randomized, active-controlled, open-label study of approximately 1,500 patients randomized 1:1 to apixaban or usual care (parenteral heparin and/or oral anticoagulation with VKAs (goal INR 2.0-3.0, excluding other NOACs; **Figure 1**). Anticoagulation is administered from randomization until 30 days following cardioversion. If cardioversion is not performed, anticoagulation will be administered for a maximum of 90 days. Clinical data including cardioversion details, efficacy and safety outcomes, length of in-hospital stay, and information regarding image guidance are collected. The apixaban dose is 5 mg BID, with a dose reduction to 2.5 mg BID if at least two of the following exist: age $\geq$ 80 years, weight $\leq$ 60 kg, or serum creatinine $\geq$1.5 mg/dL. Five doses of apixaban will be administered prior to cardioversion to achieve steady state blood levels. If an immediate cardioversion is planned, a single 10 mg dose (or 5 mg if the dose is down-titrated) is administered at least 2 hours prior to cardioversion to more rapidly bring exposure up to steady state. Investigators will use their local label for dose adjustment guidance for subjects with renal impairment.

Subjects randomized to apixaban will transition from their pre-existing anticoagulant (oral and/ or parenteral) of less than 48 hours as follows. For subjects receiving a VKA, apixaban is started when the INR is below 2.0. For all NOACs, discontinue the drug and begin apixaban at the next scheduled dose, but no earlier than 12 hours after the previous oral anticoagulant administration.

For low molecular weight heparin, apixaban should be started at the time of the next scheduled dose and no earlier than 12 hours after the previous parenteral anticoagulation administration. For intravenous infusion of unfractionated heparin, apixaban should be started immediately to 2 hours after IV UFH has been stopped.

For subjects randomized to usual therapy, stop NOAC and start warfarin immediately, and start heparin at the time of the next dose of the novel agent and continue until the INR is above 2. In general patients will be managed according the local clinician's usual practice and in a manner consistent with the design of the study.

Statistical Considerations

There was no precedent for evaluating anticoagulation-naïve patients in the setting of cardioversion. The warfarin-naive cohort from the ARISTOTLE study[14] was considered the closest data set to the patients being recruited into this study. The incidence of stroke and systemic embolism within 30 days after randomization was 0.3% (1 stroke or systemic embolism on apixaban and 3 events on usual care). The incidence for major bleeding was 0.45 (2 events on apixaban and 5 events on usual care). To adequately power for non–inferiority, 480 endpoints would be needed (similar to ARISTOTLE [15]). In this study, follow up is limited to 30 days following cardioversion or 90 days' post-randomization. An estimated event rate of approximately 1% would require 48,000 subjects, a number far in excess of practicality. The figure of 1,500 patients was considered clinically meaningful and achievable. Kaplan-Meier curves of the time to first adjudicated stroke or systemic embolism, first major bleeding event, and composite of first major bleed and clinically relevant non-major bleed as well as all-cause death will be generated.

Executive Committee

The Executive Committee (EC) comprises five academic experts, four sponsor representatives (non-voting) and a biostatistician. The EC takes sole responsibility for the study design, trial management, data analysis, and writing of the manuscript. The EC reviews recommendations from the Data Monitoring Committee and oversees the presentation and publication of the results. The EC is aided by a Clinical Research Organization and by designated national leaders in both cardiology and emergency medicine in the participating countries. This trial is sponsored

by Bristol-Myers Squibb and Pfizer. The authors acknowledge the editorial assistance of Ms. Paulette Trent.

Data Monitoring Committee

An independent Data Monitoring Committee (DMC) is responsible for monitoring the safety of subjects in the study and recommending alterations of the study to the EC and the sponsor. The sponsor forwards decisions, which may include aggregate analyses of endpoint events and safety data that are not endpoints, to regulatory authorities as appropriate.

STUDY PROCEDURES (Figure 2)

Screening

The investigator or designee at each participating clinical site obtains written informed consent from each participant, as well as contact and demographic information, relevant medical history, CHA_2DS_2VASc score, and evaluates clinical laboratory results. The patient must meet inclusion and exclusion criteria, including electrocardiographic confirmation of heart rhythm (**Table 2**). This table additionally compares the inclusion and exclusion criteria from the first completed trial of rivaroxaban (X-VeRT)[16] and a second ongoing trial of edoxaban (ENSURE-AF)[17] that, like EMANATE, prospectively evaluate novel anticoagulants in the setting of cardioversion.

Randomization

Randomization uses a centralized interactive voice-response system (IVRS). Study medication is dispensed in accordance with local policies and procedures, with accounting recorded on case report forms (CRFs). Patients can be randomized and cardioverted on the same day, combining Visits 1 and 2.

Cardioversion

The following details are recorded for each cardioversion attempted: time and date attempted, whether pharmacological, electrical, both pharmacological and electrical, or spontaneous, local investigator interpretation of image guidance, type of image guidance, number, date, and time of cardioversion attempts, rhythm status after cardioversion, and adverse events.

Compliance

Compliance with apixaban is based on pill counts at the time of cardioversion and at the end of the study. For patients randomized to usual care, compliance is assessed by INR monitoring.

Image Guidance

In the event TEE or CT imaging identifies atrial thrombus, cardioversion is deferred for at least 3 weeks. Assigned anticoagulation continues and imaging is repeated to confirm resolution of thrombus prior to cardioversion. We encourage investigators to continue assigned medication in patients identified with thrombus and repeat imaging studies after 3 weeks.

Management of Bleeding

Anticoagulation is interrupted in the event of clinically significant bleeding and managed according to local practice, which may include such measures as surgical hemostasis, volume repletion, transfusion of blood products and for patients in the conventional therapy arm, administration of protamine and supplemental Vitamin K fresh frozen plasma as deemed appropriate by the treating physician. An antidote to apixaban is in development but is not yet approved.[18]

Treatment Transitions

At the end of the study or upon early withdrawal from the study, the patient's subsequent management and treatment are conducted by the treating physician according to usual practice. When an alternative anticoagulation strategy is necessary, the protocol recommends the transition procedures contained in the apixaban package insert.[13]

Subject Withdrawal

Subjects may withdraw from the study at any time upon request, at the discretion of the investigator or sponsor for safety or behavioral reasons, or due to the inability of the subject to comply with the required schedule of visits or procedures. Subjects withdrawn from the study are subsequently managed according to conventional practice. Every effort will be made to ensure follow-up for outcomes relevant to the trial objectives.

ASSESSMENT

Clinical outcomes

Clinical outcomes are assessed by local investigators to determine whether a protocol-specified outcome had occurred. Events are recorded and reviewed by independent adjudicators blinded to treatment allocation. The clinical outcomes are the occurrence of acute stroke, systemic embolism, all-cause death, major bleeding, and clinically relevant non-major bleeding.

Acute Stroke

Stroke is defined as a focal neurological deficit of sudden onset, lasting at least 24 hours, not due to a readily identifiable non-vascular cause. Strokes are classified as primary ischemic, hemorrhagic, infarction with hemorrhagic conversion, or of unknown type if no imaging is available in accordance with definitions established by the American College of Cardiology (ACC).[19] A diagnosis of primary hemorrhagic stroke requires documentation by imaging of hemorrhage in the cerebral parenchyma or in the subdural or subarachnoid space or evidence of hemorrhage obtained by lumbar puncture, neurosurgery or identified at autopsy. Non-hemorrhagic stroke is a focal neurological deficit resulting from thrombosis or embolism evident at 24 hours. Infarction with hemorrhagic conversion requires absence of hemorrhage on initial scan but evidence of hemorrhage on subsequent scan. Stroke of unknown type is designated when brain imaging is not available.

Extracranial Systemic Embolism

Systemic embolism is defined by a clinical presentation consistent with acute loss of blood supply to an anatomical site supplied by a single artery, supported by evidence from angiography, surgical specimens, autopsy, or other objective testing.

Major Bleeding

Clinically overt bleeding is defined as visible bleeding, or signs or symptoms suggestive of bleeding with confirmatory imaging that detects the presence of blood (e.g., ultrasound, CT, or magnetic resonance). The definition of major bleeding adapted from the International Society on Thrombosis and Hemostasis (ISTH)[20] requires clinically overt bleeding accompanied by one or more of the following: a decrease in hemoglobin (Hgb) of $\geq$2 g/dL; transfusion of $\geq$2 units of packed red blood cells; bleeding that occurs in at least one of the following critical sites: intracranial, intra-spinal, intraocular (within the corpus of the eye; thus, a conjunctival bleed is

not an intraocular bleed), pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; or bleeding that is fatal.

Clinically Relevant Non-Major Bleeding

The definition of clinically overt bleeding in the EMANATE protocol is adapted from the ISTH guidelines.[21] Clinically relevant non-major bleeding is overt bleeding that compromises hemodynamics, leads to hospitalization, produces subcutaneous hematoma >25 cm^2, or 100 cm^2 if traumatic, intramuscular hematoma documented by ultrasonography, epistaxis lasting >5 minutes or repetitive (i.e., two or more episodes of bleeding within 24 hours or leads to intervention (e.g., packing or electrocoagulation); gingival bleeding occurring spontaneously (i.e., unrelated to eating or tooth brushing) or lasting >5 minutes; spontaneous macroscopic hematuria lasting >24 hours after instrumentation (e.g., catheter placement or surgery); macroscopic gastrointestinal hemorrhage, including at >1 episode of melena or hematemesis, if clinically apparent and hemoptysis outside the context of pulmonary embolism; or any other bleeding considered to have clinical consequences such as medical intervention, unscheduled contact (visit or telephone call) with a physician, temporary interruption of study drug, or associated with pain or impaired activities of daily life.

Length of Hospital Stay

The date and time of each hospital admission and discharge will be recorded.

ADVERSE EVENTS

An adverse event (AE) is defined as any untoward medical occurrence or worsening of a pre-existing medical condition in a subject administered an anticoagulant during the course of the study.

Serious Adverse Events

Serious adverse events (SAEs) are untoward medical occurrence that are life-threatening or fatal, require inpatient hospitalization or prolong an existing hospitalization, result in persistent or significant disability or incapacity, congenital anomaly or birth defect, require intervention to prevent permanent impairment or damage, or based on medical judgment are important medical

events that place a subject in jeopardy and require medical or surgical intervention to prevent one of the aforementioned outcomes.

Discussion

The novelty of this trial is the exclusive enrollment of anticoagulant-naïve patients with recently detected AF with a focus on enrolling those patients amenable to early cardioversion. Also unique, if an immediate cardioversion is planned, is the administration of a loading dose of 10 mg (or 5 mg, if the dose is down-titrated) of apixaban at least 2 hours prior to cardioversion. This is done to more rapidly achieve a steady state of anticoagulation. For this reason, potential participants are being actively identified in hospital Emergency Departments. Image-guided cardioversion with TEEs or CT scans is of special interest. Thus the Assessment of Cardioversion Use in Transesophageal Echocardiography(ACUTE) study[6], a multicenter, randomized trial comparing a TEE-guided strategy of abbreviated therapeutic anticoagulation with intravenous unfractionated heparin started 24 hours before cardioversion against conventional warfarin (INR 2.0-3.0) for at least 3 weeks before cardioversion, provided important background information. The investigators enrolled 1,222 patients with AF of >2 days' duration and found no significant difference between the two strategies in the rate of thromboembolic events over an 8-week period. The rate of hemorrhagic events was lower in the TEE-guided group (18 events [2.9%] vs 33 events [5.5%], p=0.03). The TEE group had a shorter time to cardioversion (mean ± SD, 3.0±5.6 vs. 30.6±10.6 days). The authors concluded that the strategy of TEE-guided treatment was a safe and effective alternative to the conventional treatment strategy.[6]

Additional data relevant to cardioversion derive from a post-hoc subgroup analysis of the ARISTOTLE trial, in which 540 subjects underwent 743 cardioversions and were followed for 30 days following cardioversion. No stroke or systemic embolic events occurred in patients randomized to apixaban or warfarin. One major bleeding event and two deaths were observed in each group.[10] All subjects undergoing cardioversion in that trial had been chronically anticoagulated prior to cardioversion so there was no information on the safety of apixaban in subjects newly presenting with AF or in those patients naïve to anticoagulation in whom early cardioversion is indicated. The EMANATE trial is designed to fill this important information gap.

The first and largest post-hoc analysis of cardioversion was in the RE-LY trial, which found similarly low event rates in groups treated with warfarin or either of two doses of dabigatran, 150 mg BID or 110 mg BID.[7] The analysis provided grounds for optimism regarding the potential use of a NOAC in this setting (**Table 1**). Subsequently, secondary analysis of the ROCKET-AF trial described a similar experience with rivaroxaban in a smaller number of patients insofar as event rates were low (**Table 1**).[11] The ENGAGE-AF trial of edoxaban also included patients undergoing cardioversion, but the data are not currently available.

The only prospective trial to specifically address cardioversion was the X-VERT trial, which tested rivaroxaban against usual therapy.[12] Site investigators decided whether to randomize subjects to early (1-5 days after randomization) or delayed cardioversion (between 21-56 days after randomization). Event rates were low in both arms, with a non-significant trend favoring rivaroxaban. Another ongoing prospective trial, ENSURE-AF, is evaluating edoxaban against usual care in patients with AF undergoing cardioversion.[17]

Limitations

EMANATE is an ongoing open-label trial. There is precedent for conducting open-label anticoagulation trials with blinded adjudication.[12, 17, 23-25] The outcomes of these completed trials are very similar to those of completed double-blind trials,[10,11,25,26] thus confirming the validity of this type of trial design.

We also describe the difficulty of conducting a statistically valid non-inferiority trial in the setting of cardioversion because of the very large sample size required because of low event rates reported in all the recent cardioversion trials evaluating novel agents. This limitation was recognized in the design of the comparable X-VeRT and ENSURE-AF trials. We did consider a cohort study using apixaban alone with comparison to historic controls; however, the unique feature of EMANATE is the anticoagulation-naïve population for which a historical control group would not be available. There is evidence that apixaban is being used in the setting of cardioversion in certain sites without direct evidence to support this approach. We do believe that this study fills an important data gap and that the results of this study should bear importantly upon future clinical practice.

REFERENCES

1. Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation. 2004;110:1042-6.

2. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014; 64: e1-76.

3. Arnold AZ, Mick MJ, Mazurek RP, et al. Role of prophylactic anticoagulation for direct current cardioversion in patients with atrial fibrillation or atrial flutter. J Am Coll Cardiol. 1992; 19:851-5.

4. Weinberg DM, Mancini J. Anticoagulation for cardioversion of atrial fibrillation. Am J Cardiol. 1989; 63:745-6.

5. Bjerkelund CJ, Orning OM. The efficacy of anticoagulant therapy in preventing embolism related to D.C. electrical conversion of atrial fibrillation. Am J Cardiol. 1969; 23:208-16.

6. Klein AL, Grimm RA, Murray D, et al.; for the Assessment of Cardioversion Using Transesophageal Echocardiography Investigators. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. N Engl J Med. 2001; 344: 1411-20.

7. Nagarakanti R, Ezekowitz MD, Oldgren J, et al. Dabigatran versus warfarin in patients with atrial fibrillation: An analysis of patients undergoing cardioversion. Circulation. 2011; 123:131-6.

8. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J. 2012; 33:2719-47.

9. You JJ, Singer DE, Howard PA, et al.; American College of Chest Physicians. Antithrombotic therapy for atrial fibrillation: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141 (2 Suppl): e531S-75S.

10. Flaker G, Lopes RD, Al Khatib SM, et al. Efficacy and safety of apixaban in patients after cardioversion for atrial fibrillation: insights from the ARISTOTLE trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation). J Am Coll Cardiol. 2014; 63: 1082-1087.

11. Piccini JP, Stevens SR, Lokhnygina Y, et al. Outcomes following cardioversion and atrial fibrillation ablation in patients treated with rivaroxaban and warfarin in the ROCKET AF trial. J Am Coll Cardiol. 2013; 61: 1998-2006

12. Cappato R, Ezekowitz MD, Klein AL, et al.; X-VeRT investigators. Rivaroxaban vs. Vitamin K antagonists for cardioversion in atrial fibrillation. Eur Heart J. 2014; 35: 3346-55.

13. Eliquis (apixaban) [package insert]. Princeton, NJ and New York, NY; Bristol-Myers Squibb and Pfizer; Issued December 2012.

14. ARISTOTLE study data on file; submitted to U.S. Food and Drug Administration

15. Granger CB, Alexander JH, McMurray JJ, et al.; ARISTOTLE Committee and investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011; 365: 981-92.

16. Ezekowitz MD, Cappato R, Klein AL, et al. Rationale and design of the eXplore the efficacy and safety of once-daily oral riVaroxaban for the prEvention of caRdiovascular events in patients with nonvalvular aTrial fibrillation scheduled for cardioversion trial: A comparison of oral rivaroxaban once daily with dose-adjusted vitamin K antagonists in patients with nonvalvular atrial fibrillation undergoing elective cardioversion. Am Heart J. 2014; 167:646-52

17. Lip GY, Merino J, Ezekowitz M, et al. A prospective evaluation of edoxaban compared to warfarin compared to warfarin in subjects undergoing cardioversion undergoing cardioversion: The EdoxabaN vs. warfarin in subjectS UndeRgoing cardiovErsion in atrial fibrillation study (ENSURE-AF study). Am Heart J. 2015; 169: 597-604.

18. Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. N Engl J Med. 2015 Dec 17;373(25):2413-24. doi: 10.1056/NEJMoa1510991

19. Hicks KA, Tcheng JE, Bozkurt B, et al. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). J Am Coll Cardiol 2015;66:403-69.

20. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005 Apr; 3(4):692-4.

21. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S; For the Subcommittee on Control of Anticoagulation. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost 2015; 13: 2119–26.

22. Stroke Prevention in Atrial Fibrillation Study. Final results. Circulation 84: 527–539

23. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. The BostonArea Anticoagulation Trial for Atrial Fibrillation Investigators. N Engl J Med. 1990 Nov 29;323(22):1505-11.

24. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139-51. doi: 10.1056/NEJMoa0905561.

25. Ezekowitz MD, Bridgers SL, James KE, et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. N Engl J Med. 1992 Nov 12;327(20):1406-12.

26. Giugliano RP, Ruff CT, Braunwald E, et al.; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013 Nov 28;369(22):2093-104. doi: 10.1056/NEJMoa1310907.

Figure 1. EMANATE study design

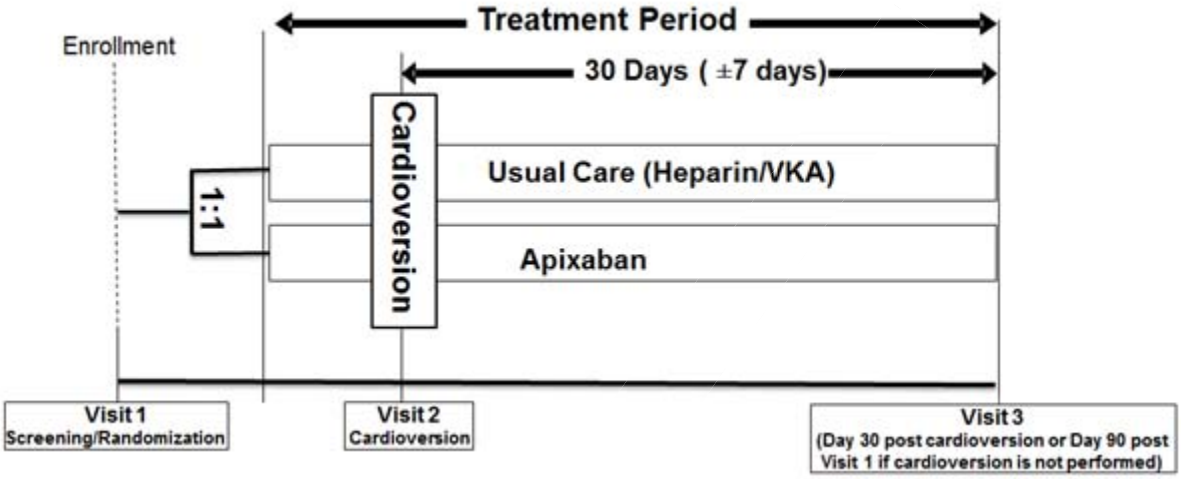

Figure 2. Subject flow

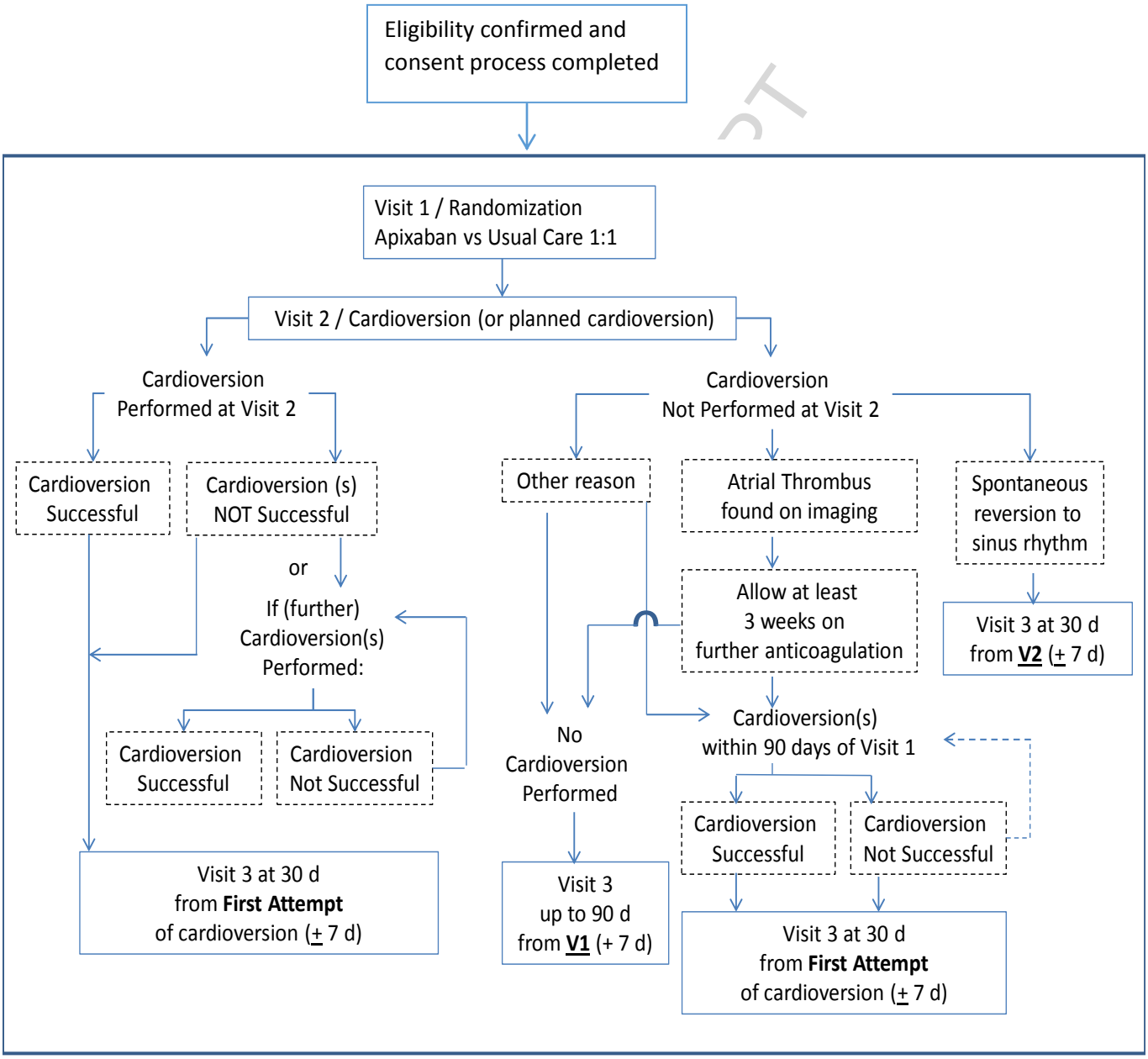

Table 1. Clinical outcome event rates within 30 days post-cardioversion in RE-LY[7], ARISTOTLE[10], and ROCKET-AF[11] studies

	RE-LY dabigatran 150 mg	RE-LY dabigatran 110 mg	RE-LY warfarin	ARISTOTLE apixaban	ARISTOTLE warfarin	ROCKET-AF* rivaroxaban	ROCKET-AF* warfarin
Stroke† or systemic embolism	0.30	0.77	0.60	0	0	1.88	1.86
Major bleeding ‡	0.60	1.70	0.60	0.30	0.20	18.75	13.04
Death§	n/a	n/a	n/a	0.6	0.5	1.88	3.73

* ROCKET-AF combined event rates for cardioversion and ablation procedure

† Both ischemic and hemorrhagic strokes

‡ ROCKET-AF combined major and non-major clinically relevant bleeding

§ RE-LY did not report death rates within 30 days of cardioversion

Table 2. Inclusion criteria for EMANATE, X-VeRT, and ENSURE-AF

EMANATE	**X-VeRT**	**ENSURE-AF**
Subjects with non-valvular atrial fibrillation (as documented by electrocardiogram (ECG) at Visit 1) indicated for cardioversion and initiation of anticoagulation in accordance with the approved local label. Subjects presenting with atrial flutter with no evidence of atrial fibrillation are not eligible for enrolment.	Hemodynamically stable nonvalvular AF > 48 hours or of unknown duration	Ongoing nonvalvular AF lasting for at least 48 hours but ≤ 12 months
Age ≥18 years (Age ≥ 19 years for Korea only and Age ≥ 20 years for Japan only)	Men or women aged > 18 y	Male or female subjects older than the minimum legal adult age (country specific)
Written informed consent	Written informed consent	Signed informed consent form
The subject is willing to provide contact details for at least one alternate person for study staff to contact regarding their whereabouts, should the subject be lost-to-follow-up over the course of the study. (Subject to IRB/IEC approval)	Scheduled for cardioversion (electrical or pharmacological) of nonvalvular AF	Ongoing nonvalvular AF at the time of randomization should be confirmed by any electrical tracing (e.g., routine 12-lead electrocardiogram [ECG], Holter monitor rhythm strip, intracardiac electrogram, or pacemaker) prior to randomization.
Female subjects of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 28 days after the last dose of assigned treatment.	Women of childbearing potential and men must agree to use adequate contraception when sexually active	Duration and proof of AF during the previous 12 months can be confirmed by any electrical tracing or a recording in the subject's medical records (e.g., medical chart, hospital discharge summary)
Subjects who are willing and able to		Symptomatic subjects with no known

comply with scheduled visits, treatment plan, and other study procedures.	history of AF and no prior electrical tracing or recording of/about the cardiac rhythm available for the past 12 months may be randomized into the study if there is reasonable belief that the current episode of AF lasts for at least 48 hours and no longer than 12 months
	Subject is planned for electrical cardioversion
	Subjects with AF following a cardiac surgical procedure (including catheter ablation) will be allowed into the study providing that they meet all the other inclusion criteria AND the time from the surgery to randomization is no less than 30 days.
	The Investigator will be responsible for assessment of risks relevant to the cardioversion procedure in such subjects.

Table 2. Exclusion criteria for EMANATE, X-VeRT, and ENSURE-AF

EMANATE	**X-VeRT**	**ENSURE-AF**
Having taken more than 48 hours of an anticoagulant (oral and/or parenteral) immediately prior to randomization.	Severe, disabling stroke (modified Rankin score of 4-5, inclusive) within 3 months or any stroke within 14 days before the randomization visit	AF considered to be of a transient or reversible nature (such as in myocarditis, post-surgery [unless the duration of AF post-cardiac surgery is N 30 days, refer to inclusion criterion #4], ionic disturbances, thyrotoxicosis, pneumonia, severe anemia etc.)
Contraindications to apixaban or usual care (eg, VKA) in accordance with the approved local label	Transient ischemic attack within 3 days before randomization	Subjects with a history of left atrial appendage (LAA) closure (either by surgery or by a procedure)
Severe hemodynamically compromised subjects requiring emergent cardioversion	Acute thromboembolic events or thrombosis (venous/arterial) within the last 14 days before randomization	Subjects with acute myocardial infarction, stroke, acute coronary syndrome, or percutaneous coronary intervention within the previous 30 days or receiving DAPT regardless of when the event has occurred
Hemodynamically significant mitral stenosis, mechanical or biological prosthetic valve or valve repair.	Acute MI within the last 14 days before randomization	Subjects with moderate or severe mitral stenosis, mitral valve rheumatic disease, unresected atrial myxoma, or a mechanical heart valve (subjects with bioprosthetic heart valves and/or valve repair can be included) and/or other conditions, such as pulmonary embolism, considered to be a formal indication for conventional anticoagulation -However subjects with AF and valvular heart diseases such as mitral valve prolapse, mitral valve regurgitation, and aortic valve

		disease are allowed in the study
Conditions other than atrial fibrillation that require chronic anticoagulation (eg, a prosthetic heart valve).	Cardiac-related criteria (known presence of left atrial/LAA thrombus before study inclusion, known presence of atrial myxoma, known left ventricular or aortic thrombus, valvular heart disease [either hemodynamically significant mitral valve stenosis or prosthetic heart valve])	Known presence of a thrombus in LAA, left atrium, left ventricle, aorta or intracardial mass
Simultaneous treatment with both aspirin and a thienopyridine (eg, clopidogrel, ticlopidine, prasugrel) or simultaneous treatment with both aspirin and ticagrelor	Active bleeding or high risk of bleeding contraindicating anticoagulant therapy	Signs of bleeding or conditions associated with high risk of bleeding including major surgeries or biopsies in the last 10 days
Pregnant females; breastfeeding females; females of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after last dose of investigational product.	Concomitant drug therapies: -Indications for anticoagulant therapy for a condition other than AF (e.g., VTE) -Chronic ASA therapy>100 mg daily or dual antiplatelet therapy -Concomitant use of strong inhibitors of both CYP3A4 and P-gp (ie, all HIV protease inhibitors and the following azole antimycotic agents: ketoconazole, itraconazole, voriconazole, posaconazole, if used systemically)	Subjects with any contraindication to anticoagulant agents
Participation in other studies involving investigational drug(s) (Phases 1-4) within	Concomitant conditions:	Subjects with conditions associated with high risk of bleeding such as a past history of

30 days before the current study begins and/or during study participation. Note: Subjects cannot be randomized into this study more than once.	-Childbearing potential without proper contraceptive measures, pregnancy, or breastfeeding -Hypersensitivity to investigational treatment or comparator treatment -Calculated CrCl <30 mL/min -Hepatic disease associated with coagulopathy leading to a clinically relevant bleeding risk -Severe conditions leading to life expectancy of < 6 months -Planned invasive procedure with potential for uncontrolled bleeding (including major surgery or cardiac catheterization) -Inability to take oral medication -Ongoing drug addiction or drug abuse	intracranial (spontaneous or traumatic), spontaneous intraocular, spinal, retroperitoneal or intra-articular bleeding; overt gastrointestinal bleeding or active ulcer within the previous year; recent severe trauma, major surgery, or deep organ biopsy within the previous 10 days; active infective endocarditis; uncontrolled hypertension (blood pressure [BP] above 170/100 mmHg); or hemorrhagic disorder including known or suspected hereditary or acquired bleeding or coagulation disorder
Severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.	Any other contraindication listed in the local labeling for the comparator treatment or experimental treatment	Subjects receiving dual antiplatelet therapy (eg, aspirin plus thienopyridine such as clopidogrel, prasugrel or ticagrelor) or anticipated to receive such therapy

Investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the Investigator, or subjects who are BMS/Pfizer employees directly involved in the conduct of the trial	Participation in a study with an investigational drug or medical device within 30 days before randomization	Subjects receiving prohibited concomitant medications (fibrinolytics, non-study anticoagulants other than those used as a bridge to/from study drug), chronic oral or parenteral Non-Aspirin/Non-Steroidal Anti-Inflammatory Drugs (NSAID) use for ≥ 4 days/week
	Previous randomization in this study	Subjects receiving chronic cyclosporine therapy
	Inability to comply with the study procedures	Subjects with active liver disease or persistent (confirmed by repeat assessments at least a week apart) elevation of liver enzymes/bilirubin: Alanine transaminase or aspartate transaminase ≥3× upper limit of normal (ULN); Total bilirubin (TBL) ≥ 2× ULN (however, subjects whose elevated TBL is due to known Gilbert's syndrome may be included in the study);
		Subjects with renal failure (end stage renal disease, calculated CrCl b15 mL/min);
		Subjects with hemoglobin b10 g/dL or platelet count b100,000 cells/mcL or white blood cell count b3000 cells/mcL;
		Subjects with pre-planned invasive procedures (other than routine endoscopy) or surgeries in which bleeding is anticipated during the study period;

Subjects who received any investigational drug or device within 30 days prior to randomization, or plan to receive such investigational therapy during the study period;
Women of childbearing potential without proper contraceptive measures, and women who are pregnant or breast feeding Note: Childbearing potential without proper contraceptive measures (ie, a method of contraception with a failure rate <1% during the course of the study (including the observational period). These methods of contraception according to the note for guidance on non-clinical safety studies for the conduct of human trials for pharmaceuticals (CPMP/ICH/286/95, modification) include consistent and correct use of hormone containing implants and injectables, combined oral contraceptives, hormone containing intrauterine devices, surgical sterilization, sexual abstinence, and vasectomy for the male partner);
Subjects with the following diagnoses or situations: -Active cancer undergoing chemotherapy, radiation or major surgery within in the next 3 months;

-Significant active concurrent medical illness or infection; Life expectancy b6 months;
Subjects who are unlikely to comply with the protocol (eg, uncooperative attitude, inability to return for subsequent visits, and/or otherwise considered by the Investigator to be unlikely to complete the study
Subjects with a known drug or alcohol dependence within the past 12 months as judged by the Investigator
Subjects with any condition that, in the opinion of the Investigator, would place the subject at increased risk of harm if he/she participated in the study